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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/16, C07D 211/66

A1

(11) International Publication Number: WO 98/37877

(43) International Publication Date: 3 September 1998 (03.09.98)

(21) International Application Number: PCT/US98/02987

(22) International Filing Date: 17 February 1998 (17.02.98)

(30) Priority Data:
08/806,728 27 February 1997 (27.02.97) US

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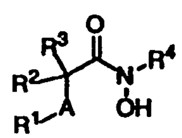
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: N-HYDROXY-2-(ALKYL, ARYL OR HETEROARYL SULFANYL, SULFINYL OR SULFONYL)-3-SUBSTITUTED ALKYL, ARYL OR HETEROARYLAMIDES AS MATRIX METALLOPROTEINASE INHIBITORS

(57) Abstract



(I)

Matrix metalloproteinases (MMPs) are a group of enzymes that have been implicated in the pathological destruction of connective tissue and basement membranes. These zinc containing endopeptidases consist of several subsets of enzymes including collagenases, stromelysins and gelatinases. TNF-α converting enzyme (TACE), a pro-inflammatory cytokine, catalyzes the formation of TNF-α from membrane bound TNF-α precursor protein. It is expected that small molecule inhibitors of MMPs and TACE therefore have the potential for treating a variety of disease states. The present invention provides low molecular weight, non-peptide inhibitors of matrix metalloproteinases (MMPs) and TNF-α converting enzyme (TACE) for the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, diabetes (insulin resistance) and HIV infection having formula (I) wherein R^2 and R^3 form a heterocyclic ring and A is S, S(O), or $S(O)_2$, and R^1 and R^4 are defined herein.

EV 311408213 US

Atty. Docket No. 01136/1/US
Serial No. 10/603,441
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N-HYDROXY-2-(ALKYL, ARYL, OR HETEROARYL SULFANYL, SULFINYL OR SULFONYL)-3-SUBSTITUTED ALKYL, ARYL OR HETEROARYLAMIDES AS MATRIX METALLOPROTEINASE INHIBITORS

BACKGROUND OF THE INVENTION

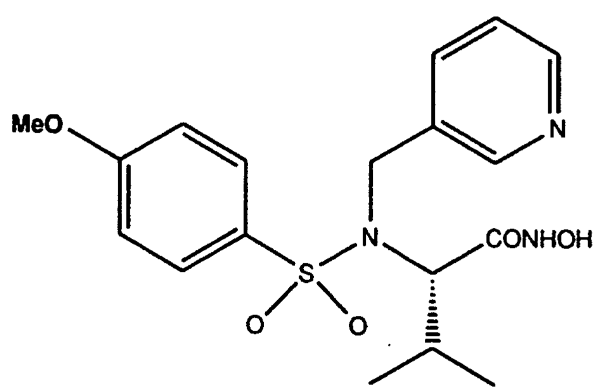
Matrix metalloproteinases (MMPs) are a group of enzymes that have been implicated in the pathological destruction of connective tissue and basement membranes. These zinc containing endopeptidases consist of several subsets of enzymes including collagenases, stromelysins and gelatinases. Of these classes, the gelatinases have been shown to be the MMPs most intimately involved with the growth and spread of tumors. It is known that the level of expression of gelatinase is elevated in malignancies, and that gelatinase can degrade the basement membrane which leads to tumor metastasis. Angiogenesis, required for the growth of solid tumors, has also recently been shown to have a gelatinase component to its pathology. Furthermore, there is evidence to suggest that gelatinase is involved in plaque rupture associated with atherosclerosis. Other conditions mediated by MMPs are restenosis, MMP-mediated osteopenias, inflammatory diseases of the central nervous system, skin aging, tumor growth, osteoarthritis, rheumatoid arthritis, septic arthritis, corneal ulceration, abnormal wound healing, bone disease, proteinuria, aneurysmal aortic disease, degenerative cartilage loss following traumatic joint injury, demyelinating diseases of the nervous system, cirrhosis of the liver, glomerular disease of the kidney, premature rupture of fetal membranes, inflammatory bowel disease, periodontal disease, age related macular degeneration, diabetic retinopathy, proliferative vitreoretinopathy, retinopathy of prematurity, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, ocular angiogenesis/neo-vascularization and corneal graft rejection. For recent reviews, see: (1) Recent Advances in Matrix Metalloproteinase Inhibitor Research, R. P. Beckett, A. H. Davidson, A. H. Drummond, P. Huxley and M. Whittaker, Research Focus, Vol. 1, 16-26, (1996), (2) Curr. Opin. Ther. Patents (1994) 4(1): 7-16, (3) Curr. Medicinal Chem. (1995) 2: 743-762, (4) Exp. Opin. Ther. Patents (1995) 5(2): 1087-110, (5) Exp. Opin. Ther. Patents (1995) 5(12): 1287-1196.

TNF-α converting enzyme (TACE) catalyzes the formation of TNF-α from membrane bound TNF-α precursor protein. TNF-α is a pro-inflammatory cytokine that is now thought to have a role in rheumatoid arthritis, septic shock, graft rejection, cachexia, anorexia, inflammation, congestive heart failure, inflammatory disease of the central nervous system,

inflammatory bowel disease, insulin resistance and HIV infection in addition to its well documented antitumor properties. For example, research with anti- TNF-α antibodies and transgenic animals has demonstrated that blocking the formation of TNF-α inhibits the progression of arthritis. This observation has recently been extended to humans as well.

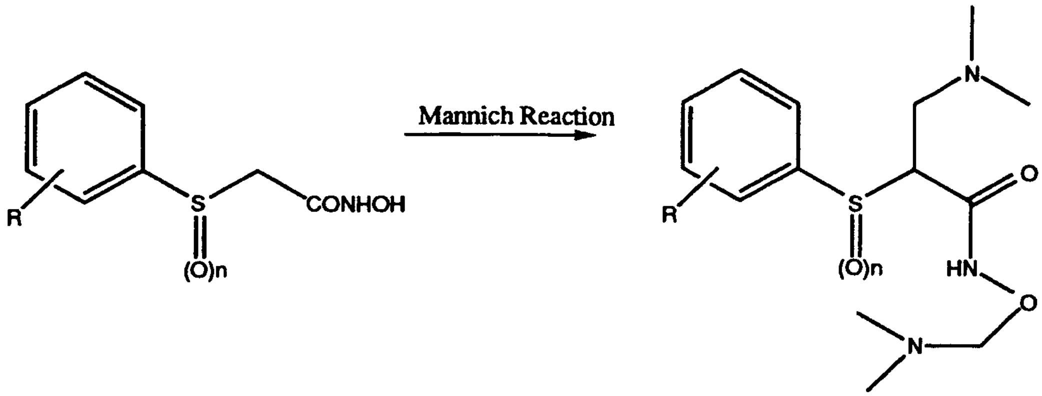
It is expected that small molecule inhibitors of MMPs and TACE therefore have the potential for treating a variety of disease states. While a variety of MMP and TACE inhibitors have been identified and disclosed in the literature, the vast majority of these molecules are peptidic and peptide-like compounds that one would expect to have bioavailability and pharmacokinetic problems common to such compounds that would limit their clinical effectiveness. Low molecular weight, potent, long acting, orally bioavailable inhibitors of MMPs and/or TACE are therefore highly desirable for the potential chronic treatment of the above mentioned disease states.

Recently, two references have appeared (U.S. 5,455,258 and European Patent Appl. 606,046) that disclose arylsulfonamido-substituted hydroxyamic acids. These documents cover compounds exemplified by CGS 27023A. These are the only non-peptide matrix metalloproteinase inhibitors disclosed to date.



CGS 27023A

Salah et al., Liebigs Ann. Chem. 195, (1973) discloses some aryl substituted thio and aryl substituted sulfonyl acetohydroxamic acid derivatives of general formula 1. These compounds were prepared to study the Mannich reaction. Subsequently, they were tested for their fungicidal activity.



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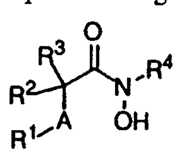
Some sulfone carboxylic acids are disclosed in U.S. patent 4,933,367. Those compounds were shown to exhibit hypoglycemic activity.

SUMMARY OF THE INVENTION:

The present invention relates to novel, low molecular weight, non-peptide inhibitors of matrix metalloproteinases (MMPs) and TNF-α converting enzyme (TACE) for the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, diabetes (insulin resistance) and HIV infection.

In accordance with this invention there is provided a group of compounds of general formula I



I

wherein:

R^1 is alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

aryl of 6 to 10 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

cycloalkyl of 3 to 8 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR^7, optionally substituted with one or two groups selected independently from R^5;

or heteroaryl-$(CH_2)_{0-6}$- wherein the heteroaryl group is 5 to 6 membered with one or two heteroatoms selected independently from O, S, and N and may be optionally substituted with one or two groups selected independently from R^5;

A is -S-, -SO- or SO_2-;

R^2 and R^3 , taken with the carbon atom to which they are attached, form a 5 to 7 membered heterocyclic ring containing O, S or N-R^7 optionally having one or two double bonds;

R^4 is hydrogen,

alkyl of 1 to 6 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

phenyl or naphthyl optionally substituted with one or two groups selected independently from R^5;

C_3 to C_8 cycloalkyl or bicycloalkyl optionally substituted with one or two groups selected independently from R^5;

saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR^7, optionally substituted with one or two groups selected independently from R^5;

R^5 is H, C_7–C_{11} aroyl, C_2–C_6 alkanoyl, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2-C_{12} alkynyl, F, Cl, Br, I, CN, CHO, C_1-C_6 alkoxy, aryloxy, heteroaryloxy, C_3-C_6 alkenyloxy, C_3-C_6 alkynyloxy, C_1–C_6 alkoxyaryl, C_1–C_6 alkoxyheteroaryl, C_1-C_6 alkylamino-C_1-C_6 alkoxy, C_1-C_2 alkylene dioxy, aryloxy-C_1–C_6 alkyl amine, C_1-C_{12}

perfluoro alkyl, $S(O)_n$-C_1-C_6 alkyl, $S(O)_n$-aryl where n is 0, 1 or 2; OCOO C_1-C_6 alkyl, OCOOaryl, $OCONR^6$, COOH, COO C_1-C_6 alkyl, COOaryl, $CONR^6R^6$, CONHOH, NR^6R^6, $SO_2NR^6R^6$, NR^6SO_2aryl, -$NR^6CONR^6R^6$, $NHSO_2CF_3$, SO_2NHheteroaryl,SO_2NHCOaryl, $CONHSO_2$-C_1-C_6 alkyl, $CONHSO_2$aryl, SO_2NHCOaryl, $CONHSO_2$-C_1-C_6 alkyl, $CONHSO_2$aryl, NH_2, OH, aryl, heteroaryl, C_3 to C_8 cycloalkyl; or saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR^7, wherein C_1–C_6 alkyl is straight or branched, heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

R^6 is H, C_1 to C_{18} alkyl optionally substituted with OH; C_3 to C_6 alkenyl, C_3 to C_6 alkynyl, C_1 to C_6 perfluoro alkyl, $S(O)_n$-C_1–C_6 alkyl $S(O)_n$ aryl where n is 0, 1 or 2;, or COheteroaryl, wherein heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

and R^7 is C_7–C_{11} aroyl, C_2–C_6 alkanoyl, C_1-C_{12} perfluoro alkyl, $S(O)_n$-C_1-C_6-alkyl, $S(O)_n$-aryl where n is 0, 1 or 2; COO-C_1-C_6-alkyl, COOaryl, $CONHR^6$, $CONR^6R^6$, CONHOH, $SO_2NR^6R^6$, SO_2CF_3, SO_2NHheteroaryl, SO_2NHCOaryl, CONHSO-C_1-C_6-alkyl, $CONHSO_2$aryl, aryl, or heteroaryl, where aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected independently from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy; and heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or N-C_1–C_6 alkyl;

alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having from 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having from 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

arylalkyl of 7 to 16 carbon atoms, wherein aryl is optionally substituted with one or two groups selected independently from R^5;

biphenylalkyl of 13 to 18 carbon atoms, wherein biphenyl is optionally substituted with one or two groups selected independently from R^5;

arylalkenyl of 8 to 16 carbon atoms, wherein aryl is optionally substituted with one or two groups selected independently from R^5;

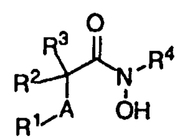
cycloalkylalkyl or bicycloalkylalkyl of 4 to 12 carbon atoms, wherein the cycloalkyl or bicycloalkyl group is optionally substituted with one or two groups selected independently from R^5;

saturated or unsaturated mono or bicyclic heterocycle containing one heteroatom selected from O, S or N-C_1–C_6 alkyl, optionally substituted with one or two groups selected independently from R^5; or

R^8R^9N-C_1-C_6-alkoxyaryl-C_1-C_6-alkyl where R^8 and R^9 are independently selected from C_1-C_6 alkyl or R^8 and R^9 together with the interposed nitrogen forms a 5-7 membered saturated heterocyclic ring optionally containing an oxygen atom, wherein the aryl group is phenyl or naphthyl;

and the pharmaceutically acceptable salts thereof.

A more preferred aspect of the present invention is the group of compounds of general formula (Ia):



Ia

wherein:

R^1 is alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

aryl of 6 to 10 carbon atoms, optionally substituted with one to two groups selected independently from R^5;

cycloalkyl of 3 to 8 carbon atoms, optionally substituted with one to two groups selected independently from R^5;

saturated or unsaturated mono or bicyclic heterocycle of from 5 to 10 members containing one heteroatom selected from O, S or NR^7, optionally substituted with one to two groups selected independently from R^5;

or heteroaryl-$(CH_2)_{0-6}$- wherein the heteroaryl group is 5 to 6 membered with one or two heteroatoms selected independently from O, S, and N and may be optionally substituted with one or two groups selected independently from R^5;

A is -S-, -SO- or SO_2-;

R^2 and R^3, taken with the carbon atom to which they are attached, form a 5 to 7 membered heterocyclic ring containing O, S or N-R^7 optionally having one or two double bonds;

R^4 is hydrogen,

alkyl of 1 to 6 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

phenyl or naphthyl optionally substituted with one or two groups selected independently from R^5;

C_3 to C_8 cycloalkyl or bicycloalkyl optionally substituted with one or two groups selected independently from R^5;

R^5 is H, F, Cl, Br, I, CN, CHO, C_7–C_{11} aroyl, C_2–C_6 alkanoyl, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_6 alkoxy, aryloxy, heteroaryloxy, C_3-C_6 alkenyloxy, C_3-C_6 alkynyloxy, C_1–C_6 alkoxyaryl, C_1–C_6 alkoxyheteroaryl, C_1-C_6-alkylamino-C_1-C_6 alkoxy, C_1-C_2-alkylene dioxy, aryloxy-C_1-C_6 alkyl amine, C_1-C_{12} perfluoro alkyl, $S(O)_n$-C_1-C_6 alkyl, $S(O)_n$-aryl where n is 0, 1 or 2; OCOO-C_1-C_6 alkyl, OCOOaryl, $OCONR^6$, COOH, COO-C_1-C_6 alkyl, COOaryl, $CONR^6R^6$, CONHOH, NR^6R^6, $SO_2NR^6R^6$, NR^6SO_2aryl, $NR^6CONR^6R^6$, $NHSO_2CF_3$, SO_2NHheteroaryl, SO_2NHCOaryl, $CONHSO_2$-C_1-C_6 alkyl, $CONHSO_2$aryl, SO_2NHCOaryl,

$CONHSO_2$-C_1-C_6 alkyl, $CONHSO_2$aryl, NH_2, OH, aryl, heteroaryl, C_3 to C_8 cycloalkyl; or saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR^7;

wherein heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected independently from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

R^6 is H, C_1 to C_{18} alkyl optionally substituted with OH; C_3 to C_6 alkenyl, C_3 to C_6 alkynyl, C_1 to C_6 perfluoro alkyl, $S(O)_n$ alkyl or aryl where n is 0, 1, or 2; or COheteroaryl;

wherein heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

and R^7 is C_7–C_{11} aroyl, C_2–C_6 alkanoyl, C_1-C_{12} perfluoro alkyl, $S(O)_n$-alkyl, $S(O)_n$-aryl where n is 0, 1 or 2; COOalkyl, COOaryl, $CONHR^6$, $CONR^6R^6$, CONHOH, $SO_2NR^6R^6$,SO_2CF_3, SO_2NHheteroaryl, SO_2NHCOaryl, $CONHSO_2$alkyl, $CONHSO_2$aryl, aryl, heteroaryl; wherein C_1–C_6 alkyl is straight or branched, heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having from 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having from 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

arylalkyl of 7 to 16 carbon atoms, wherein aryl is optionally substituted with one or two groups selected independently from R^5;

biphenylalkyl of 13 to 18 carbon atoms, wherein biphenyl is optionally substituted with one or two groups selected independently from R^5;

arylalkenyl of 8 to 16 carbon atoms, wherein aryl is optionally substituted with one or two groups selected independently from R^5;

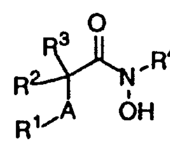
cycloalkylalkyl or bicycloalkylalkyl of 4 to 12 carbon atoms, wherein cycloalkyl or bicycloalkyl is optionally substituted with one or two groups selected independently from R^5;

saturated or unsaturated mono or bicyclic heterocycle containing one heteroatom selected from O, S or N-C_1–C_6 alkyl, optionally substituted with one or two groups selected independently from R^5;

R^8R^9N-C_1-C_6-alkoxyaryl-C_1-C_6-alkyl where R^8 and R^9 are independently selected from C_1-C_6 alkyl or R^8 and R^9 together with the interposed nitrogen forms a 5-7 membered saturated heterocyclic ring optionally containing an oxygen atom, wherein the aryl group is phenyl or naphthyl;

and the pharmaceutically acceptable salts thereof.

The most preferred group of compounds are those of the following formula (Ib):



Ib

in which

R^1 is phenyl, naphthyl, alkyl of 1-18 carbon atoms or heteroaryl such as pyridyl, thienyl, imidazolyl or furanyl, optionally substituted with C_1–C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryloxy, heteroaryloxy, C_3-C_6 alkenyloxy, C_3-C_6 alkynyloxy, halogen; or $S(O)_n$ - -C_1–C_6alkyl C_1–C_6 alkoxyaryl or C_1–C_6 alkoxyheteroaryl;

A is -S-, -SO- or -SO_2-;

R^2 and R^3 , taken with the carbon atom to which they are attached, form a 5 to 7 membered heterocyclic ring containing O, S or N-R^7 optionally having one or two double bonds;

R^4 is hydrogen,

alkyl of 1 to 6 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

phenyl or naphthyl optionally substituted with one or two groups selected independently from R^5;

C_3 to C_8 cycloalkyl or bicycloalkyl optionally substituted with one or two groups selected independently from R^5;

R^5 is H, C_7–C_{11} aroyl, C_2–C_6 alkanoyl, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2-C_{12} alkynyl, F, Cl, Br, I, CN, CHO, C_1-C_6 alkoxy, aryloxy, heteroaryloxy, C_3-C_6 alkenyloxy, C_3-C_6 alkynyloxy, C_1-C_6 alkylamino-C_1-C_6 alkoxy, C_1-C_2 alkylene dioxy, aryloxy-C_1–C_6 alkyl amine, C_1-C_{12} perfluoro alkyl, $S(O)_n$-C_1-C_6 alkyl, $S(O)_n$-aryl where n is 0, 1 or 2; OCOO C_1-C_6 alkyl, OCOOaryl, $OCONR^6$, COOH, COO C_1-C_6 alkyl, COOaryl, $CONR^6R^6$, CONHOH, NR^6R^6, $SO_2NR^6R^6$, NR^6SO_2aryl, -$NR^6CONR^6R^6$, $NHSO_2CF_3$, SO_2NHheteroaryl,SO_2NHCOaryl, $CONHSO_2$-C_1-C_6 alkyl, $CONHSO_2$aryl, SO_2NHCOaryl, $CONHSO_2$-C_1-C_6 alkyl, $CONHSO_2$aryl, NH_2, OH, aryl, heteroaryl, C_3 to C_8 cycloalkyl; saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR^7, wherein C_1–C_6 alkyl is straight or branched, heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

R^6 is H, C_1 to C_{18} alkyl optionally substituted with OH; C_3 to C_6 alkenyl, C_3 to C_6 alkynyl, C_1 to C_6 perfluoro alkyl, $S(O)_n$ alkyl or aryl where n is 0, 1 or 2; or COheteroaryl; wherein heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

and R^7 is C_7–C_{11} aroyl, C_2–C_6 alkanoyl, C_1-C_{12} perfluoro alkyl, $S(O)_n$-alkyl, $S(O)_n$-aryl where n is 0, 1 or 2; COOalkyl, COOaryl, $CONHR^6$, $CONR^6R^6$, CONHOH, $SO_2NR^6R^6$,SO_2CF_3, SO_2NHheteroaryl, SO_2NHCOaryl, $CONHSO_2$alkyl, $CONHSO_2$aryl, aryl, or heteroaryl; where aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected independently from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy; and heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or N-C_1–C_6 alkyl;

alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having from 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having from 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

arylalkyl of 7 to 16 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

biphenylalkyl of 13 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

arylalkenyl of 8 to 16 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

cycloalkylalkyl or bicycloalkylalkyl of 4 to 12 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

saturated or unsaturated mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR-C_1–C_6 alkyl, optionally substituted with one or two groups selected independently from R^5;

R^8R^9N-C_1-C_6-alkoxyaryl-C_1-C_6-alkyl where R^8 and R^9 are independently selected from C_1-C_6 alkyl or R^8 and R^9 together with the interposed nitrogen forms a 5-7 membered saturated heterocyclic ring optionally containing an oxygen atom, wherein the aryl group is phenyl or naphthyl;

and the pharmaceutically acceptable salts thereof.

The most preferred matrix metalloproteinase and TACE inhibiting compounds of this invention are:

1-benzyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide,

4-(4-methoxy-benzenesulfonyl)-1-(3-methoxy-benzyl)-piperidine-4-carboxylic acid hydroxyamide,

1-(3,4-dichlorobenzyl) -4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxamide,

4-(4-methoxy-benzenesulfonyl)-1-(4-methylbenzyl)-piperidine-4-carboxylic acid hydroxamide,

4-(4-methoxy-benzene-sulfonyl)-1-napthalene-2-yl-methylpiperidine-4-carboxylic acid hydroxamide,

1-biphenyl-4-ylmethyl-4-(4-methoxy-benzenesulfonyl)piperidine-4-carboxylic acid hydroxamide,

4-(4-methoxy-benzene-sulfonyl)-1-(3-methyl-but-2-enyl)piperidine-4-carboxylic acid hydroxamide,

1-(4-bromo-benzyl)-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide,

4-(4-methoxy-benzenesulfonyl)-1-(3-phenyl-propyl)-piperidine-4-carboxylic acid hydroxyamide,

1-tert-butyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide,

1-butyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide,

1-cyclooctyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide,

1-ethyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide,

1-isopropyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide,

1-methyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide,

1-benzyl-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide,

1-(4-fluoro-benzyl)-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide,

1-(4-fluoro-benzyl)-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide,

4-(4-methoxy-benzenesulfonyl)-1-(4-methoxy-benzyl)-piperidine-4-carboxylic acid hydroxyamide,

4-(4-methoxy-benzenesulfonyl)-1-[2-(4-methoxyphenyl)-ethyl]-piperidine-4-carboxylic acid hydroxyamide,

4-(4-methoxy-benzenesulfonyl)-1-(2-phenyl-ethyl)-piperidine-4-carboxylic acid hydroxyamide,

4-(4-n-butoxy-benzenesulfonyl)-1-(4-methoxy-benzyl)-piperidine-4-carboxylic acid hydroxyamide,

4-(4-methoxy-benzenesulfonyl)-1-(3-phenoxy-propyl)-piperidine-4-carboxylic acid hydroxyamide,

4-(4-n-butoxy-benzenesulfonyl)-1-(3-phenoxy-propyl)-piperidine-4-carboxylic acid hydroxyamide,

4-(4-methoxy-benzenesulfonyl)-1-(2-phenoxy-ethyl)-piperidine-4-carboxylic acid hydroxyamide,

4-(4-n-butoxy-benzenesulfonyl)-1-(2-phenoxy-ethyl)-piperidine-4-carboxylic acid hydroxyamide,

4-(4-methoxy-benzenesulfonyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-piperidine-4-carboxylic acid hydroxyamide,

It is understood that the definition of the compounds of formulas I, Ia and Ib, when R^1, R^2, R^3 and R^4 contains asymmetric carbons, encompass all possible stereoisomers and mixtures thereof which posses the activity discussed below. In particular, it encompasses racemic modifications and any optical isomers which possesses the indicated activity. Optical isomers may be obtained in pure form by standard separation techniques. Where not stated otherwise, the term "alkyl" refers to a straight or branched C_1–C_6 alkyl group and aryl is phenyl or naphthyl. The pharmaceutically acceptable salts are those derived from pharmaceutically acceptable organic and inorganic acids such as lactic, citric, acetic, tartaric, succinic, maleic, malonic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, and similarly known acceptable acids.

The present invention accordingly provides a pharmaceutical composition which comprises a compound of this invention in combination or association with a pharmaceutically acceptable carrier. In particular, the present invention provides a pharmaceutical composition which comprises an effective amount of compound of this invention and a pharmaceutically acceptable carrier.

The compositions are preferably adapted for oral administration. However, they may be adapted for other modes of administration, for example, parenteral administration for patients.

In order to obtain consistency of administration, it is preferred that a composition of the invention is in the form of a unit dose. Suitable unit dose forms include tablets, capsules, and powders in sachets or vials. Such unit dose forms may contain from 0.1 to 100 mg of a compound of the invention. The compounds of the present invention can be administered orally at a dose range of about 0.01 to 100 mg per kg. Such composition may be administered from 1 to 6 times a day, more usually from 1 to 4 times a day.

The compositions of the invention may be formulated with conventional excipients, such as fillers, a disintegrating agent, a binder, a lubricant, a flavoring agent, and the like. They are formulated in conventional manner.

Also according to the present invention, there are provided processes for producing the compounds of the present invention.

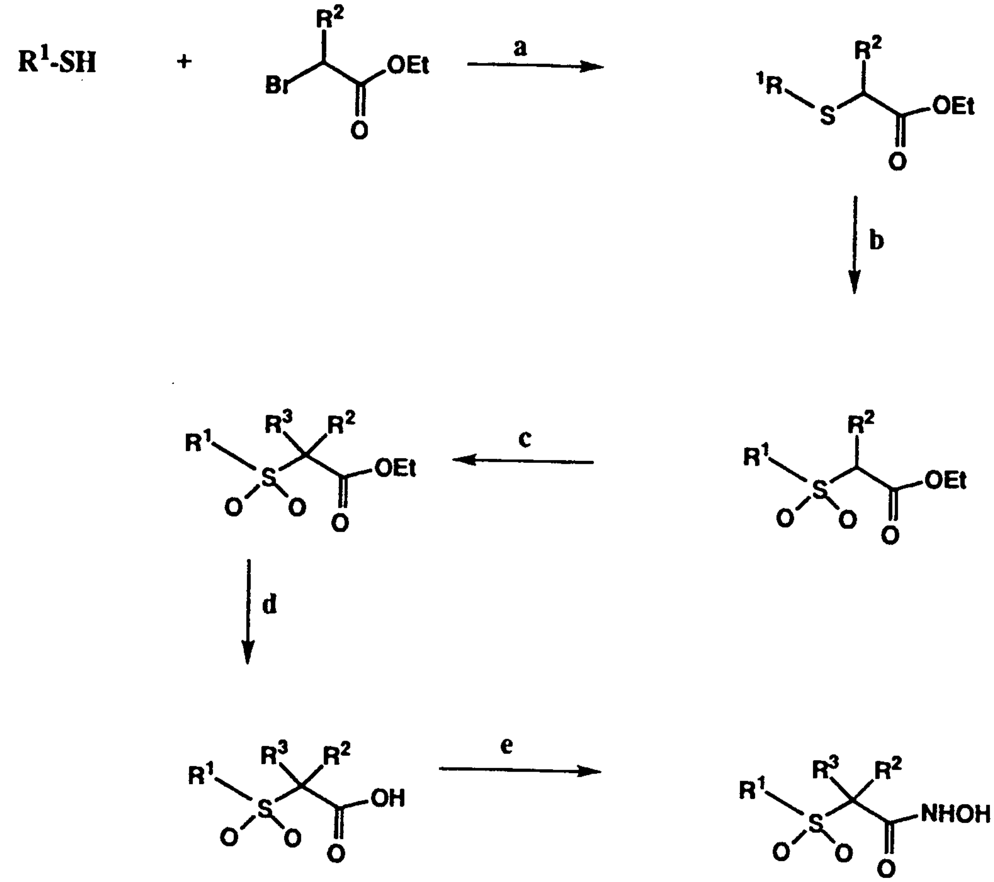
PROCESS OF THE INVENTION.

The compounds of the present invention may be prepared according to one of the general processes out lined below.

The appropriately substituted mercaptan derivative was alkylated using either substituted (Scheme I) or unsubstituted (Scheme 2) α–bromo acetic acid ester derivative in refluxing acetone using K_2CO_3 as base. The sulphide derivative thus obtained was oxidized using m-chloroperbenzoic acid in CH_2Cl_2 or by using Oxone in methanol/ water. The sulfone obtained from the above mentioned process can be either further alkylated using variety of alkyl halides to obtain the disubstituted derivative or it can be hydrolyzed using NaOH/ MeOH at room temp. However instead of using the ethyl ester, if the tertiary butyl ester is present, the hydrolysis can be carried out with TFA/CH_2Cl_2 at room temperature. Subsiquently, the carboxylic acid obtained was converted to the hydroxamic acid derivative by reaction with oxalyl chloride/ DMX (catalytic) and hydroxyl amine/ triethyl amine.

SCHEME 1

SYNTHESIS:



a. K_2CO_3/ Acetone/ Reflux; b. m-Chloroperbenzoic acid;

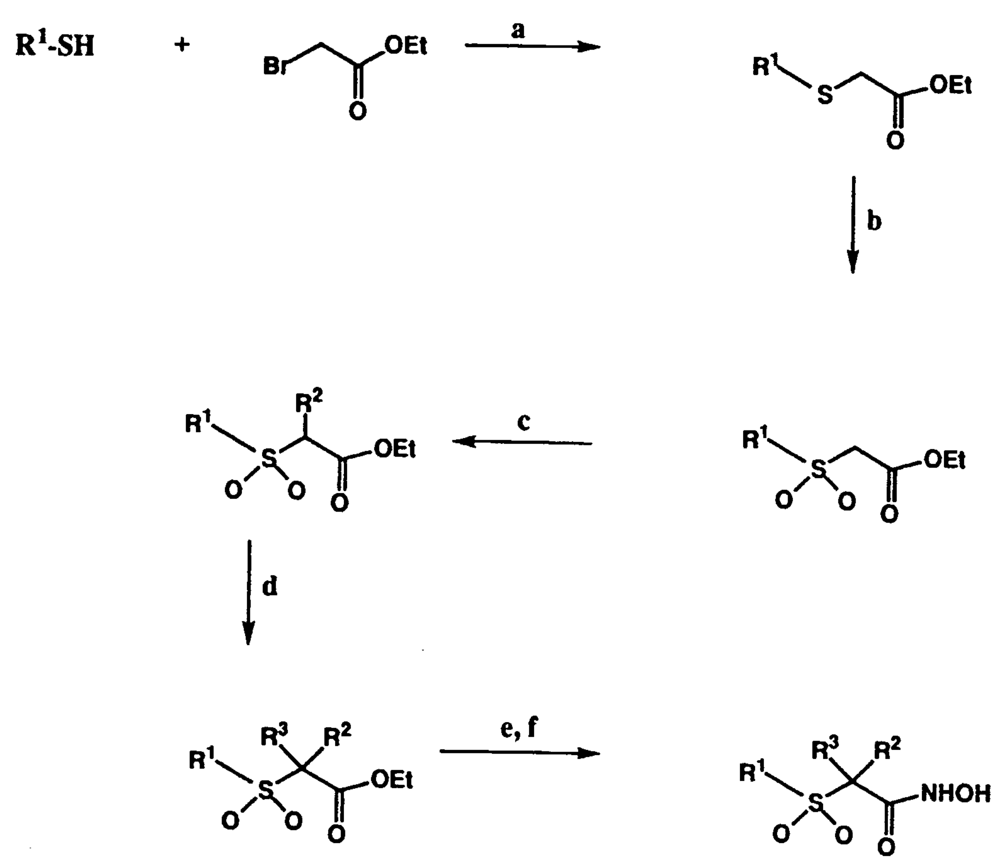
c. K_2CO_3/ 18-Crown-6/ R_3Br/Acetone/ Reflux/

d. NaOH/ MeOH/ THF/ RT

e. $(COCl)_2/CH_2Cl_2/Et_3N/NH_2OH{\cdot}HCl$.

SCHEME 2

SYNTHESIS:

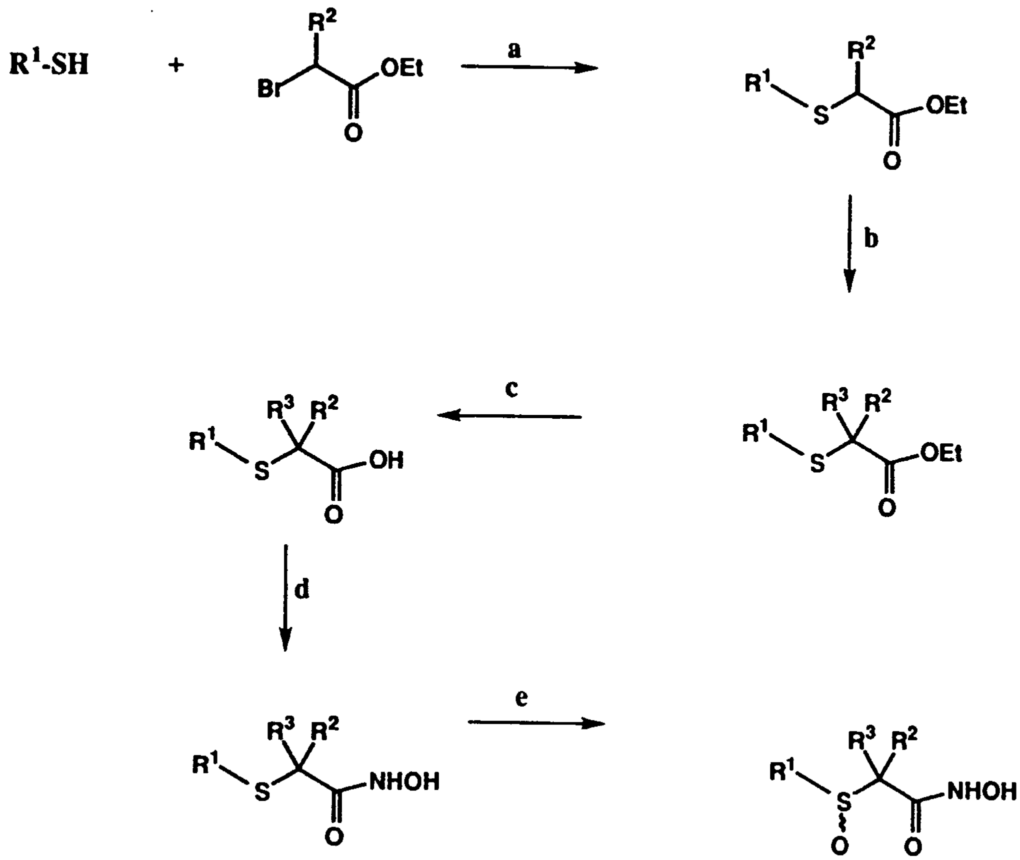


a. K_2CO_3/ Acetone/ Reflux; b. m-Chloroperbenzoic acid;
c. K_2CO_3/ 18-Crown-6/ R_2Br/Acetone/ Reflux/
d. R_3Br/ 10 N NaOH/ BzN(Et)3/ CH_2Cl_2/ RT
e. NaOH/ MeOH/ THF/ RT
f. $(COCl)_2$/CH_2Cl_2/Et_3N/NH_2OH.HCl.

As outlined in Scheme 3, the sulfide derivative can be further alkylated using lithium bis(trimethyl silyl)amide in THF at 0° C. The alkylated or mono substituted compound was hydrolyzed and converted to the hydroxamic acid derivative. The sulfinyl derivatives were prepared by oxidizing the sulfide hydroxamic acid derivatives with H_2O_2 in MeOH solution.

SCHEME - 3

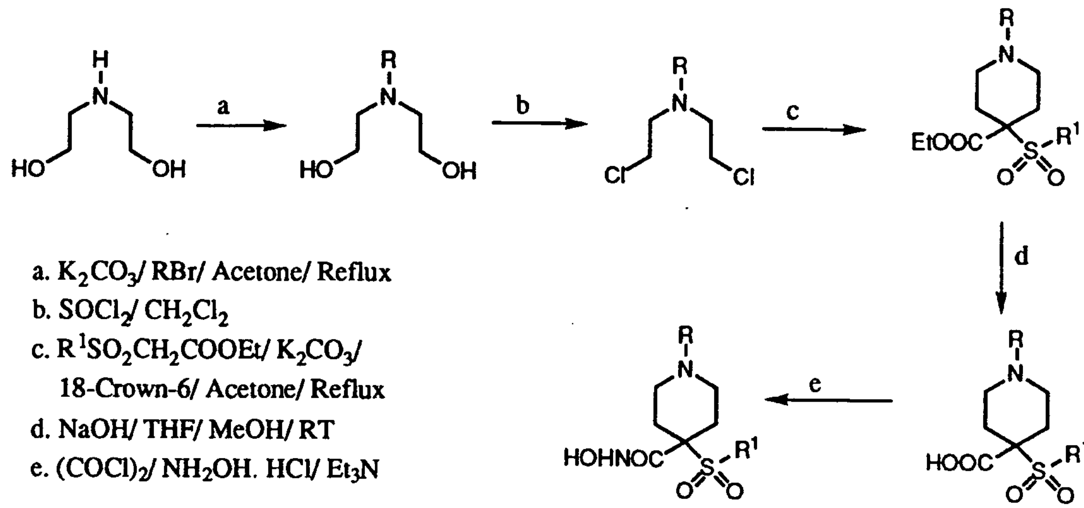
SYNTHESIS:



a. K_2CO_3/ Acetone/ Reflux; b. R_3Br/ HMDS/ THF;
c. NaOH/ MeOH/ THF/ RT
d. $(COCl)_2/CH_2Cl_2/Et_3N/NH_2OH.HCl$.
e. MeOH/ H_2O_2/ RT

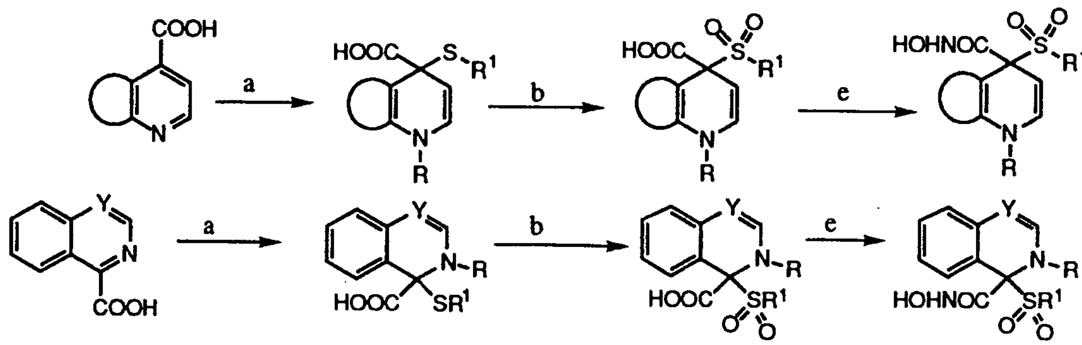
The corresponding 1-substituted-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamides were prepared starting from diethanolamine and appropriately substituted alkyl or aryl halides (Scheme 4). The N-substituted diethanol amine derivatives were converted to the dichloro compounds using thionyl chloride. The corresponding dichlorides were reacted with substituted sulfonyl acetic acid ethyl ester derivatives in the presence of K_2CO_3/18-Crown-6 in boiling acetone. 1-substituted-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid ethyl esters thus obtained were converted to the hydroxy amide as outlined in Scheme 4. Alternatively these classes of compounds and other hetrocycles can be prepared as indicated in Scheme 5 and 6.

SCHEME 4



a. K_2CO_3/ RBr/ Acetone/ Reflux
b. $SOCl_2$/ CH_2Cl_2
c. $R^1SO_2CH_2COOEt$/ K_2CO_3/ 18-Crown-6/ Acetone/ Reflux
d. NaOH/ THF/ MeOH/ RT
e. $(COCl)_2$/ NH_2OH. HCl/ Et_3N

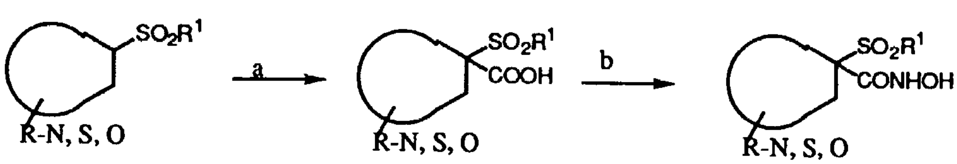
SCHEME 5



Y = N or CH

a. RBr/ R^1SH/ $CHCl^3$/ Reflux; b. Oxone/ MeOH; e. $(COCl)_2$/NH_2OH. HCl/Et_3N

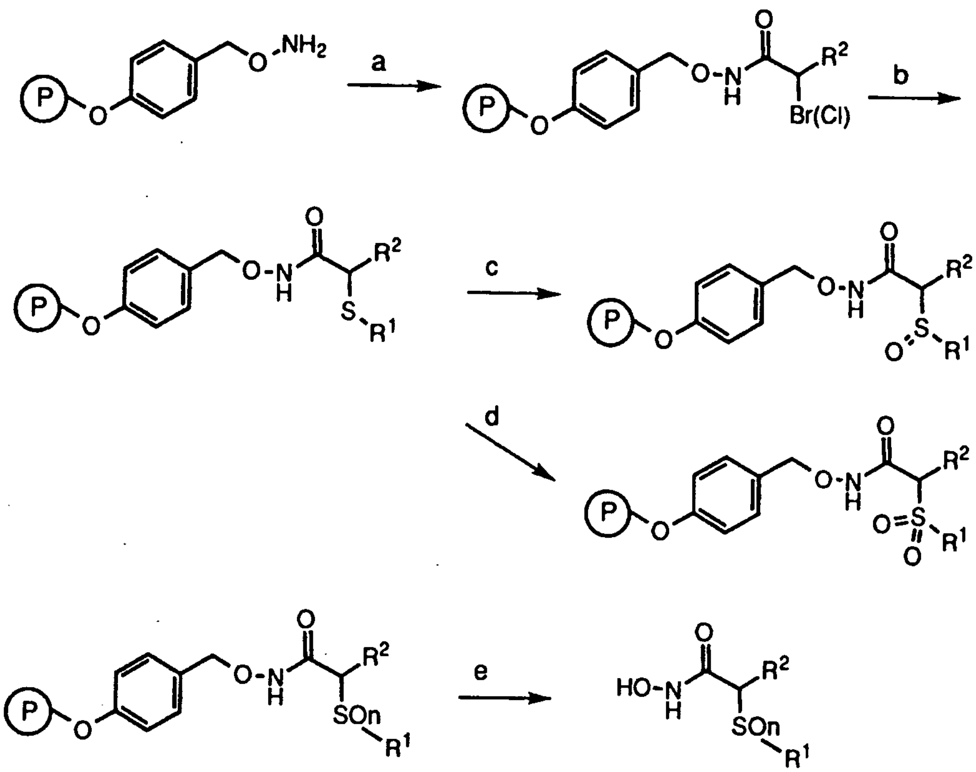
SCHEME 6



a. $LiN(TMS)_2$/ THF/ 0 °C/ CO_2; b. $(COCl)_2$/ NH_2OH. HCl/ Et_3N

Alternatively, Schemes 7 to 11 show methods for the preparation of hydroxamic acid compounds using a solid phase support (P).

Scheme 7



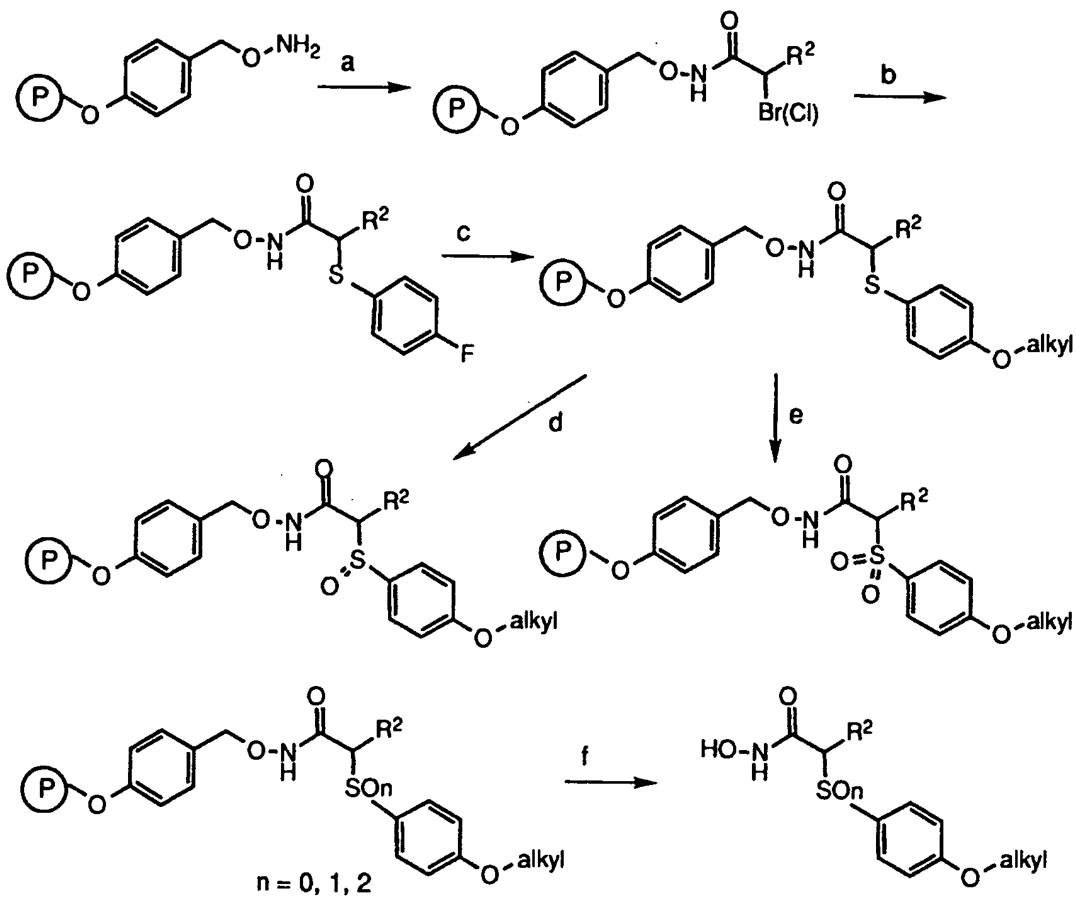
Reagents and Conditions: a) 2-Halo acid (3.0 eq.); 1-hydroxybenzotriazole hydrate (HOBt, 6.0 eq.); 1,3-diisopropylcarbodiimide (DIC, 4.0 eq.); DMF, 25°C; 2-16 hours. b) Thiol (5.0 eq.); sodium iodide (5.0 eq.); 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 3.0 eq.); THF; 25°C; 12-16 hours. c) 70% *tert*-butylhydroperoxide (40 eq.); benzenesulfonic acid (2.0 eq.); DCM; 25°C; 12-24 hours. d) mCPBA (5.0 eq.); DCM; 25°C; 12-24 hours. e) TFA : DCM (1:1); 25°C; 1 hour.

The 4-*O*-methylhydroxylamine-phenoxymethyl-copoly(styrene-1%-divinylbenzene)-resin (hydroxylamine resin) may be coupled with a 2-halo acid to give the hydroxamate ester resin. The coupling reaction may be carried out in the presence of carbodiimide, such as DIC, in an inert solvent such as DMF at room temperature. The halogen group may be displaced with a thiol in the presence of a base, such as DBU, in an inert solvent such as THF at room temperature. The sulfide may be oxidized to the sulfoxide by reaction with an oxidizing agent such as *tert*-butylhydroperoxide in the presence of an acid catalyst such as benzenesulfonic acid, in an inert solvent such as DCM at room temperature. Alternatively, the sulfide may be oxidized to the sulfone by reaction with an oxidizing agent such as *meta*-chloroperoxybenzoic

acid, in an inert solvent such as DCM at room temperature. The sulfide, sulfoxide, or sulfone may be treated with and acid, such as trifluoroacetic acid, in and inert solvent such as DCM to liberate the free hydroxamic acid.

Scheme 8 shows a method of preparing hydroxamic acids having alkoxy groups attached to the aromatic ring.

Scheme 8



Reagents and Conditions: a) 2-Halo acid (3.0 eq.); 1-hydroxybenzotriazole hydrate (HOBt, 6.0 eq.); 1,3-diisopropylcarbodiimide (DIC, 4.0 eq.); DMF, 25°C; 2-16 hours. b) 4-Fluorobenzenethiol (5.0 eq.); sodium iodide (5.0 eq.); 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 3.0 eq.); THF; 25°C; 12-16 hours. c) Alcohol (15.0 eq.); sodium hydride (15.0 eq.); DMF; 80°C; 15 hours. d) 70% *tert*-butylhydroperoxide (40 eq.); benzenesulfonic acid (2.0 eq.); DCM; 25°C; 12-24 hours. e) mCPBA (5.0 eq.); DCM; 25°C; 12-24 hours. f) TFA : DCM (1:1); 25°C; 1 hour.